NEUROLOGICAL MANIFESTATIONS IN THYROID TUMORS

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ABSTRACT

Introduction: Thyroid nodules, defined as a localized swelling of the thyroid gland may be the clinical manifestation of some order of thyroid tumors, either benign - adenomas, teratomas or malignant - carcinomas, lymphomas, sarcomas, secondary metastatic tumors.

Materials and methods: A personal five years' clinical prospective study conducted on patients with thyroid tumor nodules hospitalized in the neurology and endocrinology departments of Emergency Hospital Galati, targeted the neurological manifestations associated to thyroid tumor pathology, referring to the frequency, clinical aspect and therapeutic response to neurological determinations from thyroid tumors. Clinical and paraclinical examinations were carried out every three months. The paraclinical exam included hormone dosing, ultrasound exams, thyroid scintigraphy, biopsies, brain computed tomography and blood biochemistry tests.

Results: A large amount of detailed data was collected over a relatively long span of time.

Conclusions: The collected data largely corresponds to the reference literature. It is often the case that patients first address the neurologist, who has to diagnose the thyroid disease and its neurological manifestations.

Keywords: thyroid tumors, neurological manifestations.

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Introduction

Thyroid tumors, clinically appearing under the form of thyroid nodules, can be in histopathological terms classified as benign tumors (follicular and non follicular adenomas) and malignant (primary - epithelial and non epithelial and secondary, metastatic sites).

The thyroid nodule is defined as a localized swelling of the thyroid gland and its existence raises a suspicion of thyroid cancer, given that 95% of thyroid cancers present themselves under this form.

The frequency of thyroid nodules is 4-7% in examined subjects, but autopsy studies detect 40-50%.

Approximately 6-27% of solitary thyroid nodules are cystic, rarely with phenomena of malignant degeneration¹⁰.

There are no clinical criteria that can prove the benign or malignant nature of a thyroid nodule; the histopathological type is determined by biopsy.

Thyroid adenomas occur in 3% of the population. Clinically they present as lumps of variable sizes with clinical symptoms of hyperthyroidism or under the aspect of subclinical toxic adenoma with no signs of thyrotoxicosis.

Thyroid cancer is the most common cancer of the endocrine system. Although rare, the mortality rate in this pathology exceeds the mortality rate from all the other cancers of the endocrine system.
combined, except the ovarian cancer.

Affecting mostly women, it has an incidence which has increased in the last decade.

Thyroid cancer has a low incidence, accounting for just 1.3% of all cancer types and 0.3% of deaths by neoplastic disease. 5-10% of solitary thyroid nodules and 10-15% of the “cold” nodules detected on scintigraphy are thyroid cancer(1).

Clinical studies support that the goiter or benign thyroid nodules increase the risk of developing thyroid cancer in women by 6 times and by 38 times in men(1).

Statistically, thyroid cancer has an incidence of 4% before the age of 20, 20% for ages 20-40, 35% for ages 40-60 and 41% for people over 60 years old.

Among the histopathological types of thyroid cancer, we mention papillary carcinoma, follicular carcinoma, Hurthle cell carcinoma, medullary carcinoma, anaplastic undifferentiated carcinoma, malignant thyroid lymphoma. Thyroid cancers that can produce metastasis in the thyroid gland are: breast cancer, bronchial cancer and malignant melanoma.

The pathogenesis of thyroid cancer includes radiation, widely recognized as the sole pathogenic factor: Iodine isotope I131, I132 and I133. Other possible factors involved are the pre-existence of an autoimmune Hashimoto thyroiditis, alcoholism and genetic component(1).

The prognosis is better for forms well differentiated, papillary or follicular, and age seems to be an important prognostic factor, which is better in patients under 40 years old at whom there is no extracapsular extension or vascular invasion. Proper therapy assures survival rates of 90-99%.

Given the high frequency of patients with thyroid nodules which associate neurological signs and symptoms, we conducted a clinical study supported by laboratory examinations which had the purpose to determine the neurological manifestations of thyroid tumors referring to frequency, clinical and therapeutic response of neurological determinations in this type of thyroid pathology, and revealing the diagnostic difficulties of the damage done to the nervous system by thyroid tumors.

Materials and methods

The research followed the recommended methodology for conducting the clinical and epidemiological studies.

Subjects

The study focused on a group of 23 patients with thyroid tumors who were examined in the neurology and endocrinology departments of Galati Emergency Hospital, followed for a period of five years. Patients were examined clinical and paraclinical every 3 months.

Clinical examination was associated with paraclinical tests. Paraclinical data were recorded in the observations sheets.

Data gathering

The Newcastle index was used for the clinical diagnosis of hyperthyroidism, and in the clinical assessment of the hypothyroidism the Billewicz index was used.

For the paraclinical endocrinological diagnosis were used: hormone dosage T3-triiodothyronine, FT3 (free serum triiodothyronine), T4 (thyroxine), FT4 (free serum thyroxine), TSH (adenohypophysis thyrotropin hormone), thyroid ultrasound exam and thyroid scintigraphy with Tc99m, in doses of 2mCi, thyroid biopsy with a thin needle puncture, sella turcica radiography, CT (computed tomography)-brain scan or mediastinum scan, brain magnetic resonance imaging, biochemical usual tests of blood and urine: cholesterol, hemoglobin, number of white cells, liver tests, total proteins, bilirubin, alkaline phosphatase, immunoassay, immunoelectrophoresis, lupus cells, C-reactive protein, circulating immune complexes, antithyroglobulin antibody, bone scan, electrocardiography.

For the study of neurological damage there were used: electroneuromyography data, motor conducted velocity- VCM, sensory conducted velocity, ocular fundus exam, electroencephalography, nervous and muscular biopsy with microscopic evaluation, anatomopathological exam of some parts gathered after brain excision, lung x-ray, mediastinum x-ray, bone x-ray, Doppler exam and cerebrospinal fluid -CFS study.

Processing and statistical analysis of the data: Processing and statistical data analyses were performed using specialized software. We calculated central tendency indicators (mean and standard deviation), structural indicators and frequency indicators (prevalence).

The specific objectives of the clinical trial of patients with thyroiditis were:

• Detecting the main neurological manifestations;
• Evaluating the frequency of such cases;
Identify the response of the neurological manifestations to treatment regarding this thyroid pathology.

No major sources of error have been identified in the process of data collection and analysis.

**Results**

In the group of 23 cases there were no patients that have complained initially to the neurologic service for suffering of neurological order leading to diagnosis of thyroid carcinoma but in all cases the diagnosis of thyroid neoplasm was already settled.

All 23 cases were subject to total thyroidectomy followed by radioactive iodine treatment, subsequently instituting hormone replacement therapy with various drugs (euthyrox, tiroton and levothyroxine).

**Gender distribution**

In the studied group, the presence of thyroid tumors was significantly higher in women (p<0.027), appearing in 19 cases (82.60%), compared to males where there were only 4 cases out of the 23 recorded (17.39%) (Fig 1).

**Histological forms**

Of the total cases, 22 were malignant tumors-95.65% and a case was histologically diagnosed as being a benign tumor- thyroid follicular adenoma-4.35%. The prevalence of malignant tumors, 95.65%, was significantly higher (p<0.01), compared with that of the benign tumors - 4.35% (Fig. 2).

The distribution by age group was the following (Fig 3).

- Under 20 years old - 1 case (4.35%);
- 20-29 years old - 2 cases (8.69%);
- 40-49 years old - 5 cases (21.73%);
- 50-59 years old - 7 cases (30.44%);
- 60-69 years old - 3 cases (13.05%);
- 70-79 years old - 4 cases (17.39%);
- Over 80 years old - 1 case (4.35%);

Out of the 23 cases one patient was a smoker (4.35%).

During the trial batch of patients with thyroid tumors there was one death recorded.

Distribution on urban-rural environment (Fig. 4).

- Urban - 12 cases (52.17%);
- Rural - 11 cases (47.83%);

**Histological types of thyroid tumors of the study group were represented by:**

- Thyroid follicular adenoma - 1 case (4.35%);
- Papillary thyroid carcinoma - 10 cases (43.47%);
- Thyroid follicular carcinoma - 4 cases (17.39%);
- Papillary follicular carcinoma - 5 cases (21.75%);
- Undifferentiated carcinoma (anaplastic) - 1 case (4.35%);
- Generalized lymphoma with secondary thyroid determination- 2 cases (8.69%) (Fig. 5).
Malignant thyroid tumors

- Combination of thyroid cancer with other thyroid disorders have met simultaneously in 9 cases (39.13%):
  - Basedow disease associated with thyroid carcinoma - 1 case (4.35%);
  - Thyroid carcinoma associated with multinodular/colloidocystic goiter - 8 cases (34.78%) (Fig. 6).

Associations of thyroid carcinoma with other diseases in the studied group included:

- Tumors - 9 cases (39.13%):
  - Uterine neoplasm - 1 case (4.35%);
  - Uterine fibroids - 2 cases (8.69%);
  - Ovarian cyst - 1 case (4.35%);
  - Generalized lymphoma - 2 cases (8.69%);
  - Meningioma brain tumor - 1 case (4.35%), in a patients with follicular thyroid carcinoma with extensive compact areas, with follicular sketches and invasion of the capsule which showed on the brain CT an aspect of an expanding intracranial right hemispheric process, the suspicion being of cerebral metastasis. Histopathological examination of the surgical excision piece diagnosed a meningotheelial meningioma (Fig. 7,8).
  - Prostate adenoma - 1 case (4.35%);
  - Cervical lipoma - 1 case (4.35%);
  - Deep thrombophlebitis of the leg - 1 case (4.35%);

Endocrinological and loco-regional symptoms in malignant thyroid tumors had a small scale.

In all the cases thyromegaly was associated with:

- Discrete local pain - 3 cases;
- Phenomena of compression - 3 cases with moderate dyspnea, phonation and swallowing disorders, dysphagia.
- Phenomena of thyroid hyperactivity manifested by: palpitations, tremor of the extremities, weight loss were present in 3 cases, and those of thyroid hypofunction manifested in various grades by: bradylalia, bradipsiquia, muscle cramps, acroparesthesia, headaches, vertigo appeared in 18 patients.
There were no cases in the study group of thyroid metastasis from other cancers.

The original clinical evaluation was held in a variable time interval from the onset of the condition, between 2 and 25 years, round 5 years after onset.

Patients received surgical treatment and subsequently administration of radioactive iodine and hormone replacement in all cases.

**Neuropsychiatric manifestations of thyroid malignancies encountered included**

**Cerebral manifestations**

- Psychiatric complaints were present in 20 cases, with or without clinical science of hypothyroidism and they reduced after increasing the dose of thyroid hormone replacement.

We encountered

- Psychomotor agitation - 2 cases - 8.68% of the patients;
- Nervousness - 2 cases - 8.68% of the patients;
- 1 case of drug addiction - 4.35%, in a patient with papillary thyroid carcinoma, diagnosed 3 years ago and who used to administer to herself daily doses of analgesics, anti-inflammatory drugs, antidepressants because of polymorph unorganized and unanalyzed clinical and paraclinical accusations. Clinical examination with Billewicz index +- 22 were detected with clinical hypothyroidism. Cerebral MRI (magnetic resonance imaging) was normal. Clinical complaints reduced under treatment of thyroid hormone replacement properly administrated within 2 months which led in giving up self-medication;
- Depressive disorder - 3 cases - 13.04% of the patients;
- Organic personality disorder - 1 case - 4.35% of the patients;
- Sleep disorders: insomnia - 2 cases - 8.68%, sleepiness - 1 case - 4.35%;
- Suffocation - 1 case - 4.35%;
- Asthenia, adynamia - 8 cases - 34.78% (Fig. 9).

It is important to remember that among thyroid tumor cases the 86.95% were statistically significantly associated with neurological manifestations (p<0.05).

**Seizures**

- generalized tonic-chronic seizures with focal-motor onset - 1 case - 4.35% of the patients: they reveal multiple brain metastases in a case of papillary carcinoma with development for over 5 years, where there were no other secondary metastatic determinations in other organs.

Neurological examination was imposed due to the late onset of generalized tonic chronic seizures with focal motor onset, and CT brain evaluation with contrast has detected cerebral metastatic syndrome.

- Balance disorders with lateral deviation on the Romberg test - 1 case - 4.35% of patients and vertigo - 6 patients - 26.08%.
- Training headache rebellious to treatment - 8 cases - 34.78%, of which 3 cases with hemicranias character, which required brain CT in 7 cases and brain MRI - 1 case, without detecting secondary brain injuries caused by thyroid cancer which could explain the persistent symptoms and unbiased treatment.

**Extrapyramidal upper limb tremor** - 1 case - 4.35%, unrelated etiopathogenic with thyroid disorder, but reduced after increasing the dose of thyroid hormone replacement;

- Ischemic stroke in an acute stage - 2 cases - 8.68% and damaging stage - 1 case - 4.35%, signs of pseudobulbar syndrome - 1 case - 4.35%, amnesiac stroke - 1 case - 4.35%;

Thus out of all the cases with thyroid carcinoma, 2 cases were associated with ictal installed ischemic stroke, patients presenting as risk factors primary hypertension stage 2 and chronic atrial fibrillation of over 10 years.

**Isolated dysarthria** - 1 case - 4.35%, dysphagia - 2 cases - 8.68%;

- Orofacial lingual dyskinetic syndrome - 1 case - 4.35%, which was reduced by increasing the...
dose of thyroid hormone replacement which the patient was administrated after thyroidectomy.

- Episodes of time space disorientation - 1 case - 4.35%;
- Akinetic mutism - 1 case - 4.35% of the patients;
- Bradylalia - 3 cases - 13.04%;

**Peripheral nerves manifestations:**
- Sensory neuropathy, clinical and paraclinical confirmed without any other detectable cause by the usual methods at their disposal - 3 cases - 13.04%, acroparesthesia - 3 cases - 13.04%.

Patients were in euthyroid state, sensory neuropathy being interpreted in these situations as being paraneoplastic.

- Training sciatic neuralgia - 1 case - 4.35%.

It has resorted to scintigraphic evaluation in a case of undifferentiated thyroid carcinoma with a processing of 3 years, at which it was associated with rebellious sciatica to treatment, for which neurological examination was demanded. Bone scintigraphy diagnosed multiple bone metastases, notably being in this case the absence of metastases in other organs (Fig. 10).

Cases of generalized lymphoma with thyroid determination have associated headache, vertigo, upper limb tremor without showing neurological signs of outbreak. CT brain scan was normal, and in CSF there were lymphocytic pleocytosis and proteins in excess found. Patients experienced thyromegaly, pain in the thyroid region, low grade fever, pallor, shortness of breath, fatigue, adynamia, general lymphadenopathy. Thyroid scintigraphy revealed hypofunction (Fig. 11).

Pathological fixation on the left iliac wing and the ribs - rear segment - IV left and V and VII right.

**Cranial nerves manifestations**
- Trigeminal neuralgia which was excluded from possible detectable etiologies by laboratory methods at disposal - 1 case - 4.35%.
- Other manifestations:
  - Claude Bernard-Horner syndrome - 1 case - 4.35%, by latero-cervical compression phenomena by a thyroid tumor lobe.
  - Cervicalgia without bone damage - 1 case -4.35%.

In one case at the thoracic mediastinum CT, the patient presented an aspect of the superior mediastinum occupied my multiple macronodular images, around 2-2.5cm, expanding to the cervical region, close to the right thyroid lobe, with deviation of the trachea and esophagus. Histopathologically, there was a confirmed diagnosis of non-Hodgkin malignant lymphoma with secondary thyroid determination, establishing radiotherapy treatment.

**Laboratory endocrinological diagnosis included:**
- Normal biological samples, alkaline, phosphatase;
- Hormone dosages;
- X-rays and bone scans;
- Thyroid ultrasound and thyroid volume determination;
- Thyroid scintigraphy - allowed the diagnosis of thyroid carcinoma by detecting “cold” thyroid nodules;
- Post-thyroidectomy control scintigraphy registered negative aspects in patients without recurrence, scintigraphic aspect showing the lack of capturing the radioactive tracer (Fig. 12).

Histopathologic examination of the surgical excision parts, taken from the medical documenta-
tion of the patients and performed in various clinics where the interventions took place revealed histopathological aspects described above.

Laboratory neurological diagnosis included
Ocular fundus examination - 23 cases.

There were no changes detected in the ocular fundus that could be suggestive for expanding intracranial processes secondary to the thyroid cancer in none of the patients.

EEG (electroencephalography) - performed in 23 cases – was insignificant for diagnosis as there was no recorded characteristic image for the existence of brain of focal brain lesions.

X-ray evaluation
- CT brain exam - 18 cases;
- Brain MRI - 1 case;
These were imposed by:
- Training diffuse headache or hemicranias, rebellious to treatment.
- Generalized convulsive seizures and focal motor seizures, late-onset;
- Hemiparesis progressive muscular weakness;
- Ictal motor hemiparesis deficit suggestive for strokes;
- Time space disorientation episodes;
- Training vertigo, associated with unregulated equilibrium disorders, uninfluenced by therapy;
- Amnesia stroke;
- Training paresthesia syndrome in half of the body.

Among the patients examined by brain CT, 10 presented cerebral and cerebellar atrophy.

Determination of motor and sensory driving speeds

These laboratory neurological evaluations were detailed in the cases previously presented.

Of the 23 cases of thyroid tumors, 2 cases of operated adenocarcinomas presented recurrence, requiring another surgical intervention:

**Benign thyroid tumors**

In the studied group, we encountered only one case of benign thyroid tumor:

follicular thyroid adenoma in a patient of 60 years old who associated primary hypertension stage II and who presented himself in the neurology service for an episode amnesiac stroke lasting 2 hours. The thyroid scintigraphy showed catchment areas of enlarged thyroid lobes, with areas of hypocaptation – “cold” nodules in the inferior bilateral pole. Brain CT showed a wide spread cortical atrophy. Endocrinological clinical and laboratory evaluations led to the diagnosis and imposed the surgical intervention. The histopathologic examination of the thyroid tumor revealed follicular thyroid adenoma (Fig. 13).

We have not encountered neurological symptoms characteristic to this type of thyroid tumors, we didn’t find any mentions of pathognomonic neurological changes for thyroid adenomas, not even in other studies.

**Discussions**

An important thing to note is the valid statistic correlation between the data collected from the patients and the data obtained from the literature, data regarding the fact that thyroid tumor occur more often in women over the age of 40\(^1\).

The frequency of cases with thyroid determination in generalized lymphoma was higher in the tracked study group than in other studies, 1-2\%\(^1,2\).

There were no cases of medullary thyroid cancer in the studied group.
Association of the thyroid carcinoma with the goiter was more frequent in the tracked patients than in any other studies: 10-15\%\(^{(3)}\).

We haven’t met any association between thyroid carcinoma and Hashimoto’s thyroiditis, although, in the specialty literature it appears in 10\% of the cases of chronic thyroiditis\(^{(4)}\).

According to studies, bone metastases are the main cause of death in thyroid cancer - 90\% of the deaths\(^{(5)}\).

**Conclusion**

During the study of cases with thyroid cancers in patients in the pursued group, through clinical and mainly laboratory tests we were able to observe the following:

- Malignant thyroid tumors were predominant, namely papillary carcinoma, present mostly in women, age range 50-60 years, consistent with the data existing in other studies;
- Brain metastases were detected without other secondary metastases in other organs, the time interval since the onset of the disease being of only two years (other studies show cases in which the brain metastases were relevant for the thyroid neoplasm);
- Compression phenomena (cervical sympathetic chain) was met in a patient who was suffering of Claude Bernard-Horner syndrome;
- Paraneoplastic sensory neuropathy was seen in 3 patients, but without any special clinical features;
- The diagnosis of bone metastasis with a starting point in a thyroid carcinoma has been established in one case in the neurology service, from the neurological manifestations such as training sciatica neuralgia, rebellious to treatment at which bone scintigraphy detected secondary determinations in the bones;
- The thyroid carcinoma was associated with a meningothelial meningioma in a patient who presented a motor deficit with progressive emphasis, the suspicion of brain metastasis being excluded to the histopathological examination of the surgical excision piece.

A large number of thyroid cancers have been associated with other types of tumors of various organs: ovarian cysts, uterine cervical cancer, uterine fibroids, prostate adenoma.

The finding corresponds to the data from other studies which cite the association of thyroid tumors with other types of tumors of other organs and systems.

Thyroid carcinoma was associated with evolving ischemic strokes in patients who presented vascular risk factors: hypertension, atrial fibrillation, diabetes, etc;

We frequently encountered psychiatric disorders, patients showing depressive disorders, anxiety, psychomotor agitation, organic personality disorder, drug addiction, sleep disorder, adynamia, etc;

Neurological complaints under treatment - persistence of headache, vertigo, balance disorders etc. require some neuroimaging investigations like MRI, brain CT which can detect brain metastases, lacunar stroke, acute cerebral ischemia, generalized cortical atrophy, as was also the case in our study.

**References**